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Original Article

Platinum Exposure and Cause-Specific Mortality Among Patients With Testicular Cancer

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BACKGROUND: Although testicular cancer (TC) treatment has been associated with severe late morbidities, including second malignant neoplasms (SMNs) and ischemic heart disease (IHD), cause-specific excess mortality has been rarely studied among patients treated in the platinum era. **METHODS:** In a large, multicenter cohort including 6042 patients with TC treated between 1976 and 2006, cause-specific mortality was compared with general population mortality rates. Associations with treatment were assessed with proportional hazards analysis. **RESULTS:** With a median follow-up of 17.6 years, 800 patients died; 40.3% of these patients died because of TC. The cumulative mortality was 9.6% (95% confidence interval [CI], 8.5%-10.7%) 25 years after TC treatment. In comparison with general population mortality rates, patients with nonseminoma experienced 2.0 to 11.6 times elevated mortality from lung, stomach, pancreatic, rectal, and kidney cancers, soft-tissue sarcomas, and leukemia; 1.9-fold increased mortality (95% CI, 1.3-2.8) from IHD; and 3.9-fold increased mortality (95% CI, 1.5-8.4) from pneumonia. Seminoma patients experienced 2.5 to 4.6 times increased mortality from stomach, pancreatic, bladder cancer and leukemia. Radiotherapy and chemotherapy were associated with 2.1 (95% CI, 1.8-2.5) and 2.5 times higher SMN mortality (95% CI, 2.0-3.1), respectively, in comparison with the general population. In a multivariable analysis, patients treated with platinum-containing chemotherapy had a 2.5-fold increased hazard ratio (HR; 95% CI, 1.8-3.5) for SMN mortality in comparison with patients without platinum-containing chemotherapy. The HR for SMN mortality increased 0.29 (95% CI, 0.19-0.39) per 100 mg/m^2 platinum dose administered (P_{trend} < .001). IHD mortality was increased 2.1-fold (95% CI, 1.5-4.2) after platinum-containing chemotherapy in comparison with patients without platinum exposure. **CONCLUSIONS:** Platinum-containing chemotherapy is associated with a dose-dependent increase in the risk of SMN mortality. ***Cancer* 2019;0:1-12**.

KEYWORDS: cause-specific mortality, cisplatin, epidemiology, platinum, survivorship, testicular cancer.

INTRODUCTION

The prognosis of testicular cancer (TC) has greatly improved since the late 1970s because of the introduction of cisplatin-containing combination chemotherapy for disseminated TC, improvements in radiation techniques, and better supportive care.[1,2] Currently, in Europe, the 10-year TC-specific survival is higher than 95%.[1]

TC treatment may, however, cause detrimental long-term health effects for TC survivors. Previous studies have shown that radiotherapy is associated with increased morbidity[3-7] and mortality from second malignant neoplasms

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(SMNs).[6-8] A recent study from our group observed that chemotherapy was associated with SMN incidence as well.[9] Chemotherapy has been associated with increased cardiovascular disease (CVD) morbidity[10-13] and excess CVD mortality,[6,14,15] but the data are less consistent.

Few studies have assessed long-term cause-specific excess mortality after TC treatment. In a large, international cohort study including 1-year TC survivors (n = 38,907), Fossa et al[15] observed 1.4-fold increased CVD mortality after chemotherapy among patients treated between 1943 and 2002. More recently, among US patients treated between 1980 and 2010, Fung et al[14] found increased CVD mortality only in the first year after chemotherapy for nonseminoma. They also reported increased mortality due to pneumonia and influenza in comparison with the general population, whereas Fossa et al observed an increased risk of death due to fibrosis and pneumonitis.[14,15]

Since the 1980s, TC treatment intensity has gradually been reduced with decreases in the radiotherapy field size and dose among patients with seminoma, with the introduction of surveillance for stage I disease, and with fewer cycles of chemotherapy for patients with nonseminoma.[2,10,16,17] The impact of these changes on cause-specific excess mortality among more recently treated TC survivors is not yet clear. Therefore, we examined cause-specific mortality within a large, multicenter Dutch cohort of patients with TC diagnosed in the cisplatin era between 1976 and 2006.

MATERIALS AND METHODS

Study Population and Design

A hospital-based cohort was established that included 6124 patients with TC who were younger than 50 years at their TC diagnosis and were treated in 13 Dutch hospitals between 1976 and 2006 (Supporting Fig. 1).[5-8,10] The primary treatment was known for all patients. For efficiency reasons, we used a case-cohort design to facilitate detailed treatment data collection while allowing the assessment of multiple outcomes.[18] A hospital-stratified subcohort composing 15% of the base cohort (25% in the coordinating hospitals Antoni van Leeuwenhoek and University Medical Center Groningen) was randomly selected. Before the analysis, 82 patients without follow-up for vital status were excluded, and this left 6042 patients in the full cohort and 1138 patients in the randomly selected subcohort for analysis.

We established vital status up to July 2016 for 93.7% of the patients through linkage with the Dutch Central Bureau for Genealogy, which collects genealogic information on all Dutch inhabitants, including the date of death. For 378 patients (6.3%), the linkage failed, and the vital status was obtained from the patient's general practitioner (GP) and/or tumor registries. Information on the cause of death was retrieved from hospital tumor registries, the patient's medical chart, and the GP and through linkage with the nationwide cause of death registry at Statistics Netherlands up to January 1, 2016. Direct and indirect causes of death were (re)coded according to the *International Classification of Diseases, Tenth Revision*.

For all patients in the subcohort and for all patients who had developed a predefined event (SMN, including contralateral TC; ischemic heart disease [IHD]; heart failure; or diabetes mellitus) and were not part of the subcohort, detailed treatment data were abstracted from the medical charts; these data included chemotherapy regimens, cumulative doses and numbers of cycles, and radiotherapy fields and doses for primary treatment as well as relapse treatment. The study protocol was submitted to the institutional review board of the Netherlands Cancer Institute, which waived the requirement for individual patient consent.

All patients underwent an orchidectomy. For early-stage seminoma, orchidectomy was usually followed by radiotherapy,[16-19] which was typically given to the infradiaphragmatic para-aortic, ipsilateral iliac, and inguinal lymph nodes, with doses to delineated treatment fields ranging from 30 to 35 Gy. Since the mid-1980s, radiation doses have gradually decreased to 26 to 32 Gy.[19] Patients with stage II to IV seminoma and nonseminoma were primarily treated with cisplatin-containing combination chemotherapy (initially with cisplatin, vinblastine, and bleomycin and since the mid-1980s with bleomycin, etoposide, and cisplatin [BEP]).[20] Although rare, 1.8% of the patients (n = 10) in the subcohort who were treated with chemotherapy (mainly patients with nonseminoma) were treated with vinblastine, bleomycin, dactinomycin, or a combination of these drugs between 1976 and 1980. Surveillance after orchidectomy was standard treatment for stage I nonseminoma from 1984 onward in most hospitals.[21]

Statistical Analysis

The time at risk started at the TC diagnosis and ended at the date of death, the date of emigration, or January 1, 2016 (whichever came first). Mortality rates among patients with TC were compared with age-specific, calendar period–specific, and site-specific cancer mortality rates in

the Dutch male population. Standardized mortality ratios (SMRs), absolute excess mortality (expressed per 10,000 person-years), and corresponding 95% confidence intervals (CIs) were computed with standard methods and are reported for the full cohort.[18] General population mortality data from Statistics Netherlands for 1976-2015 were used as reference rates. Unless otherwise stated, TC mortality was excluded from analyses. Tests for homogeneity and trends of SMRs were performed within collapsed person-time Poisson regression models; models were adjusted for age unless specified otherwise.[22]

Missing information on stage (7.5%), primary and follow-up treatment (radiotherapy [0.8%], radiotherapy field [13.5%], radiotherapy dose [11.8%], chemotherapy [0.8%], chemotherapy regimen [5.1%], and number of cycles [11.3%]), and weight, height, and smoking status at the TC diagnosis (11.9%) were imputed for the cases and subcohort members via ordered multiple imputation by chained equations with 20 data sets and with patient clusters ignored.[19,20] Our results are based on administered chemotherapy and radiation doses. Multinomial models and linear regression models were used for imputation; the year and age at treatment, histology, age, hospital, and cause-specific cumulative hazards of mortality calculated with a Cox regression model before imputation were included as extra covariates.[20] Because of the amount of missing data on body size area and cumulative platinum dose, we based the administered platinum dose on the number of administered cycles, which agreed well with actual cumulative administered doses in milligrams per meter squared of body surface area in patients without missing data.

Cumulative mortality was estimated with death due to TC as a competing risk,[23] and trends over time were evaluated via competing risk regression models with adjustments for the age at TC diagnosis. Multivariable proportional hazards models were used to assess associations of TC treatment with cause-specific mortality. The time since TC treatment was used as the time scale, and the partial likelihood function was adjusted for the case-cohort analysis with Barlow's inverse probability weights.[18-23] Treatment was included time-dependently, and this allowed a patient to add person-time to a different treatment category at the date on which treatment for relapsed or contralateral TC was initiated.[23] All analyses were adjusted for age and smoking unless stated otherwise. For a sensitivity analysis, we evaluated the effect of clustering of patients within a treatment center by adding a clustering term to the Cox models, and we adjusted the variance for within-treatment center clustering. To assess excess relative risk by the administered treatment dose, the linear increase in the hazard ratio (HR) for dose categories (estimated from a Cox model with the category value set at the median dose within that category) was estimated via variance-weighted least squares regression with weights equal to 1/variance of the HR for each imputed data set. We assessed dose-response relationships by first modeling the cause-specific HRs as $HR = 1 + \beta(\text{dose})$, where β is the proportional increase in the HR per unit increase in dose. We evaluated a departure from linearity by including a quadratic dose term in the model $HR = 1 + \beta(\text{dose}) + \Phi(\text{dose})^2$ and testing whether the coefficient for the quadratic dose term was $\Phi = 0$. Regression model estimates were pooled with Rubin's rule.[24,25] The proportional hazards assumption was assessed with residual-based methods. Standard errors are reported as robust standard errors. A P value $\leq .05$ was considered significant. Stata statistical software (StataCorp LP, College Station, Texas; 2013) was used for analysis.

RESULTS

The cohort comprised 2875 patients with seminoma and 3167 patients with nonseminoma (Table 1 and Supporting Fig. 1). The median age of patients with seminoma was 35.0 years (interquartile range [IQR], 30.4-40.4 years), whereas the median age of patients with nonseminoma was 27.7 years (IQR, 23.3-33.6 years; $P < .001$). The median follow-up was 17.6 years (IQR, 12.2-24.2 years); 22.7% of the patients were followed 25 years or longer.

Comparisons With the General Population

The cause of death was available for 96.1% of all 800 patients who had died up to January 1, 2016 (Table 2). Of these 800 patients, 322 (40.3%) died of TC, 226 (28.3%) died of SMNs other than TC, and 104 (13.0%) died of diseases of the circulatory system. Non-TC mortality was 1.4-fold increased (95% CI, 1.3-1.6) in comparison with general population mortality rates. We observed 28.9 excess deaths from TC (95% CI, 25.8-32.3) and 13.0 excess deaths due to causes other than TC (95% CI, 9.1-17.1) per 10,000 person-years of follow-up. In the univariate analysis, SMRs for non-TC mortality decreased among older patients ($P_{\text{trend}} < .001$; Supporting Tables 1 and 2). SMRs for non-TC mortality and SMN mortality remained increased even 20 or more years after treatment in comparison with general population rates, without a clear trend in SMRs ($P_{\text{trend}} = .24$ for non-TC mortality; $P_{\text{trend}} = .49$ for SMN mortality; Supporting Table 1). Adjusted for age and follow-up duration,

TABLE 1. Baseline Characteristics for Patients With Testicular Cancer Treated Between 1976 and 2006

Characteristic	Cohort (n = 6042)	Seminoma (n = 2875)	Nonseminoma (n = 3167)
Age at diagnosis, median (IQR), y	31.7 (25.8-37.7)	35.0 (30.4-40.4)	27.7 (23.3-33.6)
Age at diagnosis, No. (%)			
<20 y	330 (5.5)	21 (0.7)	309 (9.8)
20-29 y	2269 (37.6)	657 (22.9)	1612 (50.9)
30-39 y	2381 (39.4)	1431 (49.8)	950 (30.0)
40-49 y	1062 (17.6)	766 (26.4)	296 (9.4)
Treatment period, No. (%)			
1975-1985	968 (16.0)	346 (12.0)	622 (19.6)
1986-1995	1902 (31.5)	871 (30.3)	1031 (32.6)
1996-2006	3172 (52.5)	1658 (57.7)	1514 (47.8)
Primary treatment, No. (%)			
Orchidectomy only	1450 (24.0)	401 (14.0)	1049 (33.1)
Radiotherapy ± chemotherapy[a]	2255 (37.3)	2086 (72.6)	169 (5.3)
Chemotherapy only	2337 (38.7)	388 (13.5)	1949 (61.5)
Vital status (up to January 1, 2016), No. (%)			
Alive	5145 (85.2)	2532 (88.1)	2613 (82.5)
Died	800 (13.2)	297 (10.3)	503 (15.9)
Emigrated	97 (1.6)	46 (1.6)	51 (1.6)
Follow-up, median (IQR), y	17.6 (12.2-24.2)	16.9 (12.3-23.2)	18.2 (12.1-25.3)
Follow-up, No. (%)			
<1 y	167 (2.8)	38 (1.3)	129 (5.1)
1-4 y	206 (3.4)	56 (1.9)	150 (4.7)
5-9 y	492 (8.1)	250 (8.7)	242 (7.6)
10-14 y	1456 (24.1)	805 (28.0)	651 (20.6)
15-19 y	1281 (21.2)	656 (22.8)	626 (19.7)
20-24 y	1067 (17.7)	519 (18.1)	548 (17.3)
≥25 y	1373 (22.7)	551 (19.2)	822 (26.0)
Attained age at end of follow-up, median (IQR), y	50.4 (43.0-57.8)	53.0 (46.4-60.3)	47.6 (39.2-55.2)

Abbreviation: IQR, interquartile range.
[a]One hundred sixteen patients (1.92%) had both radiotherapy and chemotherapy.

SMRs for non-TC mortality and SMN mortality did not decrease among more recently treated patients (1996-2007) in comparison with those treated between 1976 and 1985 and between 1986 and 1995 (P_{trend} = .49 for non-TC mortality; P_{trend} = .80 for SMN mortality; Supporting Table 3). However, SMRs for noncancer mortality did decrease over time ($P < .001$).

Neither SMN mortality nor IHD mortality was increased among patients treated with surgery only (Supporting Table 4). Primary radiotherapy was associated with increased SMN mortality (SMR, 2.1; 95% CI, 1.8-2.5), especially due to colorectal, pancreatic, and urologic SMNs, but not with noncancer mortality. Primary chemotherapy was also associated with increased SMN mortality (SMR, 2.5; 95% CI, 2.0-3.1) and specifically with increased mortality from lung, colorectal, and noncolorectal gastrointestinal (GI) SMNs and leukemia. The receipt of chemotherapy was also associated with a 2.1-fold increased SMR for IHD (95% CI, 1.3-3.2) and a 2.8-fold increased SMR for respiratory diseases (95% CI, 1.3-5.1).

For patients with seminoma, non-TC mortality was 1.3-fold increased (95% CI, 1.1-1.4). SMN mortality was significantly elevated (116 deaths; SMR, 1.6), particularly because of SMNs of the pancreas (18 deaths; SMR, 4.6), stomach (7 deaths; SMR, 2.5), and bladder (6 deaths; SMR, 4.4) and leukemia (6 deaths; SMR, 3.2; Table 2). Mortality due to urogenital diseases (5 deaths; SMR, 3.6) was also increased, and this mainly reflected deaths from chronic kidney diseases. For patients with nonseminoma, non-TC mortality was 1.7-fold higher than expected (95% CI, 1.5-1.9; Table 2) and did not decrease among more recently treated patients (P_{trend} = .96 for treatment period; Supporting Table 2). SMN mortality was significantly elevated (110 deaths; SMR, 2.3), particularly because of SMNs of the lungs (26 deaths; SMR, 2.0), esophagus (6 deaths; SMR, 2.8), stomach (6 deaths; SMR, 3.2), pancreas (7 deaths; SMR, 2.7), rectum (6 deaths; SMR, 4.8), and kidneys (7 deaths; SMR, 5.9), soft-tissue sarcomas (6 deaths; SMR, 11.6), and leukemia (6 deaths; SMR, 4.1; Table 2). Patients with nonseminoma also experienced increased mortality from IHD (29 deaths; SMR, 1.9) and pneumonia (6 deaths; SMR, 3.9). Additional analysis showed that the SMR for soft-tissue sarcoma was increased 7.6-fold (95% CI, 1.6-22.3) after 1 to 5 years of follow-up and 6.9-fold (95% CI, 2.2-16.2) after 5 or more years of follow-up in all TC survivors. However, these analyses are based on fewer than 10 cases.

TABLE 2. Standardized Mortality Ratios for Selected Causes of Death (≥ 5 deaths observed) Among Dutch Testicular Cancer Patients Treated Between 1976-2006[a]

		Overall				Seminoma				Nonseminoma			
Cause of Death	*ICD-10*	No.	SMR	95% CI	AEM	No.	SMR	95% CI	AEM	No.	SMR	95% CI	AEM
Any cause	A00-Y89	800	2.4	2.2-2.6	42.0	297	1.6	1.4-1.7	20.1	503	3.6	3.3-3.9	61.3
Any cause other than TC	A00-C61, C63-Y89	478	1.4	1.3-1.6	13.0	242	1.3	1.1-1.4	9.64	236	1.7	1.5-1.9	16.1
Cancer other than TC[b]	C00-C61, C63-C97	226	1.9	1.6-2.1	19.1	116	1.6	1.3-2.0	8.6	110	2.3	1.9-2.7	10.4
Long, bronchus and trachea	C33-C34	46	1.3	1.0-1.8	1.1	20	1.0	0.6-1.5	–0.1	26	2.0	1.3-2.9	2.1
GI tract SMN	C15-C26, C48	81	2.4	1.9-3.0	4.3	47	2.3	1.7-3.1	5.2	34	2.6	1.8-3.6	3.5
Noncolorectal GI SMN	C15-C17, C22-C26, C48	58	2.7	2.1-3.5	6.6	36	2.9	2.0-4.1	4.4	22	2.5	1.5-3.9	2.1
Esophagus	C15	10	1.9	0.9-3.4	0.4	4	1.2	0.3-3.0	0.14	6	2.8	1.0-6.2	0.7
Stomach	C16	13	2.8	1.5-4.8	0.8	7	2.5	1.0-5.2	0.8	6	3.2	1.2-7.0	0.7
Pancreas	C25	25	3.9	2.5-5.7	1.7	18	4.6	2.7-7.2	2.7	7	2.7	1.1-5.6	0.8
Colorectal GI SMN	C18-C21	23	1.9	1.2-2.9	2.0	11	1.5	0.8-2.7	0.7	12	2.5	1.3-4.4	1.2
Colon	C18	13	1.5	0.8-2.5	0.4	7	1.3	0.5-2.7	0.3	6	1.7	0.6-3.7	0.4
Rectosigmoid, rectum and anus	C19-C21	10	3.2	1.6-5.9	0.6	4	2.2	0.6-5.5	0.41	6	4.8	1.8-10.5	0.8
Melanoma (skin)	C43	5	1.3	0.4-3.0	0.1	3	1.4	0.3-4.2	0.2	2	1.2	0.1-4.3	0.1
Soft-tissue sarcomas	C46-47, C49	8	7.2	3.1-14.1	0.6	2	3.3	0.4-12.1	0.3	6	11.6	4.3-25.3	0.9
Kidney (without renal pelvis)	C64	9	3.0	1.4-5.8	0.5	2	1.1	0.1-4.0	0	7	5.9	2.4-12.3	1.0
Urinary bladder	C67	9	4.0	1.8-7.6	0.6	6	4.4	1.6-9.6	0.9	3	3.4	0.7-10.1	0.4
Non-Hodgkin lymphoma	C82-C85	7	2.0	0.8-4.0	0.3	3	1.5	0.3-4.3	0.2	4	2.6	0.7-6.8	0.4
Leukemia	C91-C96	12	3.6	1.9-6.3	0.8	6	3.2	1.2-7.0	0.8	6	4.1	1.5-8.8	0.8
Unspecified and unknown primary malignancies	C76, C80	20	4.1	2.5-6.3	1.4	8	3.7	1.2-5.4	1.0	12	6.1	3.2-10.7	1.7
Noncancer deaths	A00-B99, E00-Y89	247	1.2	1.1-1.4	3.7	124	1.1	0.9-1.3	1.6	123	1.4	1.1-1.6	5.6
Circulatory system	I00-I99	104	1.3	1.0-1.5	1.6	53	1.1	0.8-1.4	0.8	51	1.5	1.1-2.0	3.0
IHD	I20-I25	51	1.4	1.0-1.8	2.5	22	1.0	0.6-1.5	–0.4	29	1.9	1.3-2.8	2.4
Myocardial infarction	I21-I22	41	1.4	1.0-1.9	0.7	16	0.9	0.5-1.5	–0.2	25	2.1	1.4-3.1	2.2
Other ischemic diseases	I20,23-25	10	1.2	0.6-2.3	0.2	6	1.2	0.4-2.6	0.2	4	1.3	0.3-3.2	0.1
Other heart diseases	I30-33, I39-52	25	1.2	0.8-1.7	0.2	13	1.0	0.6-1.8	0.2	12	1.4	0.7-2.4	0.5
Cerebrovascular disease	I60-I69	10	0.8	0.4-1.5	–0.2	7	0.9	0.4-1.9	–0.1	3	0.6	0.1-1.7	–0.4
Other circulatory diseases[c]	I00-15,I26-28, I34-38, I70-99	18	1.6	0.9-2.5	0.7	11	1.6	0.8-2.9	0.8	7	1.5	0.8-3.5	0.4
Respiratory diseases	J00-J99	19	1.3	0.8-2.1	0.4	9	1.0	0.5-2.0	0.1	10	1.8	0.8-3.3	0.7
Pneumonia	J12-J18	9	2.4	1.1-4.5	0.5	3	1.3	0.3-3.9	0.1	6	3.9	1.5-8.4	0.8
COPD and asthma	J40-J47	8	1.0	0.4-2.0	0.1	5	1.0	0.3-2.4	0.0	3	1.0	0.2-2.9	0.0
Infectious diseases	A00-B99	8	1.2	0.5-2.4	0.1	4	1.1	0.3-2.9	0.1	4	1.3	0.4-3.4	0.2
Urogenital system[d]	N00-N99	7	3.0	1.2-6.2	0.4	5	3.6	1.2-8.4	0.7	2	2.1	0.3-7.7	0.2
Digestive system	K00-K93	11	0.8	0.4-1.4	–0.2	6	0.8	0.3-1.6	–0.4	5	0.9	0.3-2.1	–0.1
Symptoms and signs[e]	R00-R99	45	2.3	1.7-3.1	2.3	17	1.6	0.9-2.6	1.2	28	3.2	2.2-4.7	3.3
External causes (accidents, suicide, homicide)	V01-Y89	34	0.8	0.6-1.2	–0.6	18	0.9	0.6-1.5	–0.2	16	0.8	0.4-1.2	–0.8
Suicide	X60-X84	15	0.8	0.4-1.2	–0.4	6	0.6	0.2-1.3	–0.7	9	0.9	0.4-1.7	–0.2

Abbreviations: AEM, absolute excess mortality (Observed-Expected/10.000 person-years); CI, confidence interval; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; *ICD-10*, *International Classification of Diseases, Tenth Revision*; IHD, ischemic heart disease; SMN, second malignant neoplasm; SMR, standardized mortality ratio; TC, testicular cancer.

[a]Cause-specific mortality was reported if ≥5 deaths were observed among all TC survivors.

[b]322 patients died due to TC (SMR:811, 95%CI:725-905,AER: 28.9), 55 seminoma (SMR: 316, 95%CI:238-411,AER:10.5) and 267 non-seminoma patients (SMR:1199, 95%CI:1060-1352,AER: 45.2), respectively.

[c]Patients had the following cause of death: Other circulatory diseases (19 patients): rheumatic fever (I100), hypertensive renal disease (I12), Pulmonary embolism (I26), valve disorders (I34, I35), endocarditis (I38), atherosclerosis or aortic aneurysm (I70, I71), pelvic varicose veins (I86). Urogenital system (7 patients): kidney disease and disorders of the kidney or ureter.

[d]Symptoms and signs includes unknown/unspecified causes of death.

[e]Median follow-up for patients who died from soft tissue sarcoma was 10.6 years after primary TC.

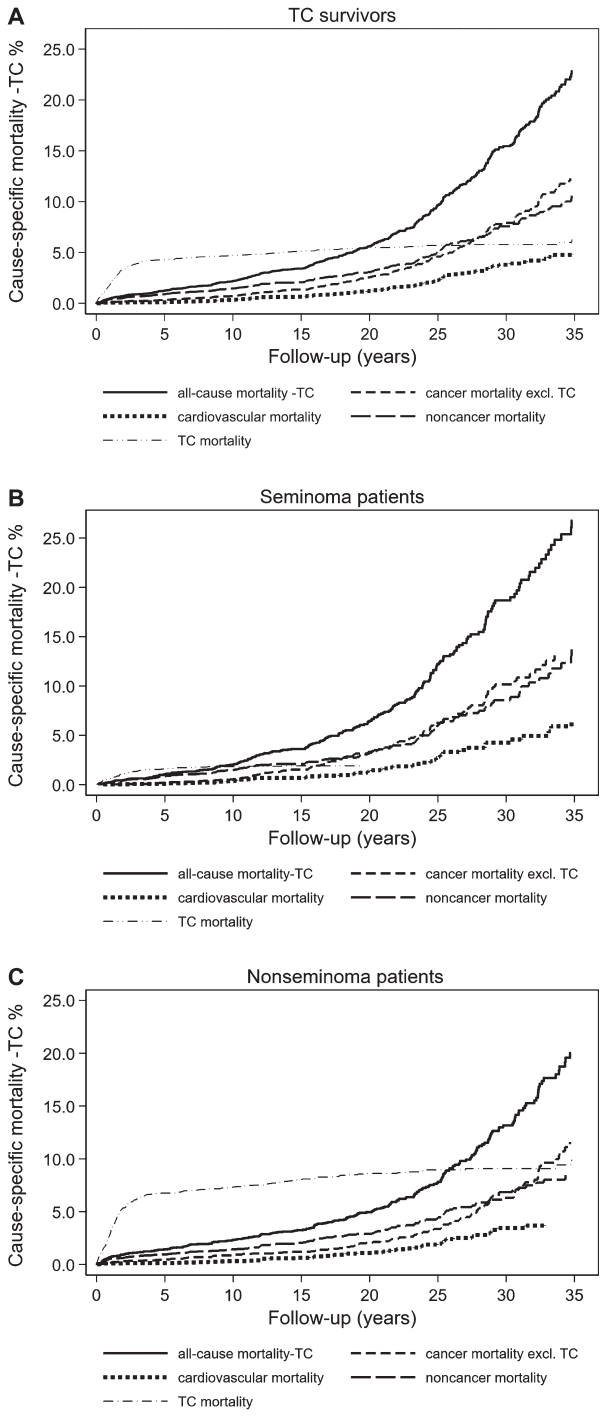

Figure 1. Cumulative mortality due to TC, all causes other than TC, second malignant neoplasms other than TC, causes other than cancer, and cardiovascular disease for (A) all patients with TC combined, (B) patients with seminoma, and (C) patients with nonseminoma. TC indicates testicular cancer.

Cumulative Mortality

The cumulative mortality was 9.6% (95% CI, 8.5%-10.7%) 25 years after TC treatment (Fig. 1). Cumulative mortality was lower for more recently treated patients (P_{trend} = .026). The 15- and 25-year SMN mortality rates were 1.2% (95% CI, 0.6%-2.0%) and 5.1% (95% CI, 3.8%-6.7%), respectively, in 1976-1985 and 2.1% (95% CI, 0.8%-1.8%) and 4.1% (95% CI, 3.2%-5.2%), respectively, in 1986-1995, whereas the 15-year cumulative mortality rate was 1.6% (95% CI, 1.1%-2.1%) in 1996-2006 (Supporting Fig. 2). Correspondingly, CVD mortality was 1.5% (95% CI, 0.9%-2.4%) and 3.7% (95% CI, 2.6%-5.0%) in 1976-1985 and 0.5% (95% CI, 0.3%-0.9%) and 1.8% (95% CI, 1.2%-2.6%) in 1986-1995 at 15 and 25 years, respectively, whereas the 15-year cumulative mortality was 1.7% (95% CI, 1.2%-2.3%) in 1996-2006. SMN mortality slightly decreased over time for both patients with seminoma (P_{trend} = .052) and patients with nonseminoma (P_{trend} = .012; Supporting Fig. 2). The 25-year cumulative mortality due to SMNs was 4.6% (95% CI, 3.9%-5.4%). The 25-year cumulative CVD mortality was low at 2.3% (95% CI, 1.8%-2.9%) and decreased among more recently treated patients (P_{trend} < .001), including both patients with seminoma and patients with nonseminoma (Supporting Fig. 2). TC mortality decreased substantially until the mid-1980s, whereafter mortality seemed to stabilize (Supporting Fig. 3).

Cause-Specific Mortality and TC Treatment: Case-Cohort Analysis

In a multivariable analysis, platinum-containing chemotherapy was associated with 2.5 times increased SMN mortality (95% CI, 1.8-3.5) in comparison with surgery only, whereas GI tract SMN mortality was 3.1-fold increased (95% CI, 1.7-5.7) among platinum-treated patients (Table 3). Both colorectal (P_{trend} = .006) and noncolorectal GI tract SMN mortality (P_{trend} < .001) increased with a higher dose of cisplatin-containing chemotherapy, with the receipt of platinum-containing chemotherapy at 400 to 499 and ≥500 mg/m^2 being associated with 2.4 and 6.4 times increased noncolorectal GI cancer mortality, respectively, in comparison with patients not receiving platinum-containing chemotherapy. A dose-response relationship was observed between SMN mortality and the cumulative administered platinum dose in particular for GI tract SMNs (Fig. 2), with the HR for mortality due to any SMN increasing linearly by 0.29 (95% CI, 0.19-0.39; P_{trend} ≤ .001) per 100 mg/m^2 administered platinum dose, whereas the HR for mortality due to GI tract SMNs linearly increased by 0.66 (95% CI, 0.35-0.99; P_{trend} ≤ .001) per 100 mg/m^2 administered platinum dose. Lung cancer mortality increased 1.9

TABLE 3. Associations Between TC Treatment and Cause-Specific Mortality: Case-cohort Analysis[a]

	SMN Mortality (n = 226)			GI Cancer Mortality (n = 81)			Colorectal Cancer Mortality (C18-C21; n = 23)			Noncolorectal GI Cancer Mortality (C15-C17, C22-C26, Excluding C48; n = 57)[b]			Lung Cancer Mortality (n = 46)			IHD Mortality (n = 51)[c]		
Characteristic	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI
CT[d,e]																		
No	128	1	Reference	48	1	Reference	14	1	Reference	34	1	Reference	27	1	Reference	26	1	Reference
Yes	98	2.67	1.92-3.70	33	3.14	1.84-5.34	9	1.81	0.62-5.28	23	3.51	1.87-6.55	19	1.92	0.91-4.07	25	2.05	1.53-4.16
Platinum-based CT[e]																		
No	152	1	Reference	48	1	Reference	14	1	Reference	34	1	Reference	29	1	Reference	28	1	Reference
Yes	73	2.54	1.82-3.53	33	3.07	1.65-5.70	9	2.16	0.69-6.75	23	3.46	1.67-7.16	17	1.29	0.60-2.80	23	1.11	0.56-2.21
Platinum-based CT dose[e]																		
No platinum-based CT	152	1	Reference	56	1	Reference	14	1	Reference	34	1	Reference	29	1	Reference	26	1	Reference
<400 mg/m^2	14	2.55	1.55-4.20	4	1.96	0.63-6.09	1	—	—	4	2.95	0.95-9.11	2	0.74	0.17-3.16	9	2.23	0.86-5.83
400-499 mg/m^2	39	2.22	1.48-3.32	11	2.46	1.21-4.97	4	1.63	0.46-5.86	7	2.44	1.02-5.84	9	1.54	0.64-3.70	8	1.02	0.39-2.66
≥500 mg/m^2	20	3.19	1.98-5.14	10	5.80	2.85-11.82	4	4.30	1.18-15.70	10	6.37	2.73-14.81	6	2.41	0.85-6.84	7	3.39	1.27-9.03
P_{trend}			<.001			<.001			.006			<.001			.076			.130
Para-aortic radiotherapy dose[f]																		
No para-aortic radiotherapy	104	1	Reference	29	1	Reference	11	1	Reference	17	1	Reference	23	1	Reference	33	1	Reference
≤26 Gy	47	0.90	0.60-1.37	18	1.66	0.81-3.41	6	0.98	0.29-3.35	12	2.18	0.87-5.51	10	0.89	0.36-2.18	7	0.41	0.15-1.16
>26-32 Gy	34	1.98	1.26-3.11	15	4.17	1.99-8.75	3	1.50	0.30-7.45	13	7.37	3.10-17.49	5	1.38	0.35-3.35	4	0.65	0.22-1.98
>32-36 Gy	9	2.24	0.88-5.66	4	5.26	1.66-16.62	2	3.99	0.53-30.18	3	6.65	1.37-32.16	4	2.17	0.32-14.65	2	1.70	0.41-7.88
>36 Gy	32	3.41	2.06-5.65	14	7.37	3.35-16.22	2	1.71	0.19-15.30	2	12.28	4.84-31.15	5	2.14	0.65-7.00	4	0.91	0.22-3.74
P_{trend}			<.001			<.001			.164			<.001			.059			.636
Radiation field and dose[f]																		
No radiotherapy	104	1	Reference	29	1	Reference	11	1	Reference	17	1	Reference	23	1	Reference	33	1	Reference
Para-aortic field, ≤26 Gy	14	0.54	0.27-1.06	3	0.59	0.15-2.32	1	0.32	0.46-5.86	2	0.73	0.11-4.91	5	1.35	0.25-7.31	3	—	—
Para-aortic field, >26 Gys	14	2.68	1.18-6.10	5	4.12	1.13-14.99	0	—	—	6	10.53	2.81-39.42	3	0.93	0.26-3.28	1	0.47	0.14-1.62
P_{trend}			.839			.213			.244			<.001			.254			.015
Dog-leg field, ≤26 Gy	32	1.38	0.88-2.17	14	2.90	1.35-6.26	5	1.63	0.46-5.86	10	3.77	1.44-9.88	6	—	—	4	0.42	0.06-3.19
Dog-leg field, >26 Gy	62	2.45	1.66-3.30	29	5.29	3.75-10.20	6	4.30	1.18-15.70	22	7.95	3.54-17.85	9	1.44	0.64-3.24	9	0.75	0.33-1.69
P_{trend}			<.001			<.001			.140			<.001			.550			.363
Supradiaphragmatic radiotherapy[g]																		
No	211	1	Reference	73	1	Reference	21	1	Reference	52	1	Reference	44	1	Reference	49	1	Reference
Yes	15	1.40	0.75-2.60	8	1.45	0.55-3.83	2	4.12	0.78-21.16	2	0.93	0.26-3.41	2	1.37	0.27-6.97	2	2.04	0.43-9.67
Smoking at TC diagnosis[h,i]																		
No	104	1	Reference	41	1	Reference	16	1	Reference	27	1	Reference	14	1	Reference	17	1	Reference
Yes	122	1.80	1.20-2.50	40	1.55	0.94-2.55	7	0.74	0.26-2.12	30	1.88	1.03-3.44	32	3.83	1.73-8.45	34	3.35	1.35-8.30

Abbreviations: CI, confidence interval; CT, chemotherapy; GI, gastrointestinal; HR, hazard ratio; IHD, ischemic heart disease; n, median number observed deaths over the 20 imputed datasets (rounded); SMN, second malignant neoplasm; TC, testicular cancer.

[a]Treatment details including relapse and CLTC treatment were incomplete for the following variables in the subcohort: radiotherapy (0.8%), radiotherapy field (13.5%), radiotherapy dose (11.8%), chemotherapy (0.8%), chemotherapy regimen (5.1%), number of cycles (11.3%), smoking at TC diagnosis (11.9%), disease stage (5.5%). In the subcohort, 54% was diagnosed with stage 1, 22.2% with stage 2, 5.19% stage 3 and 12.8% stage 4, while stage was missing in 5.5%.

[b]Non-colorectal cancer deaths include 10 esophageal malignancies, 13 stomach cancers, 25 pancreatic cancers and 9 other malignancies including small intestine, liver and bile ducts and ill-defined gastrointestinal malignancies. One malignancy of peritoneum or retroperitoneum (C48) was not included.

[c]Cardiovascular disease deaths: myocardial infarction, coronary heart disease and heart failure (decompensatio cordis).

[d]Although most testicular cancer survivors receive platinum-containing chemotherapy since 1976, some patients were treated with vinblastin, alone or combined with dactinomycin.

[e]Adjusted for age (continuous), abdominal radiation dose (continuous), supradiaphragmatic radiotherapy and smoking (at TC diagnosis).

[f]Adjusted for age (continuous), platinum dose (continuous, in steps of 100 mg/m^2 equivalent dose), supradiaphragmatic RT and smoking (at TC diagnosis).

[g]Adjusted for age (continuous), abdominal radiation dose (continuous), chemotherapy (categorical) and smoking (at TC diagnosis).

[h]Adjusted for age (continuous).

[i]No interaction was present between smoking and treatment. Lung cancer risk was borderline significantly higher for patients with RT and smoking (P interaction: 0.058).

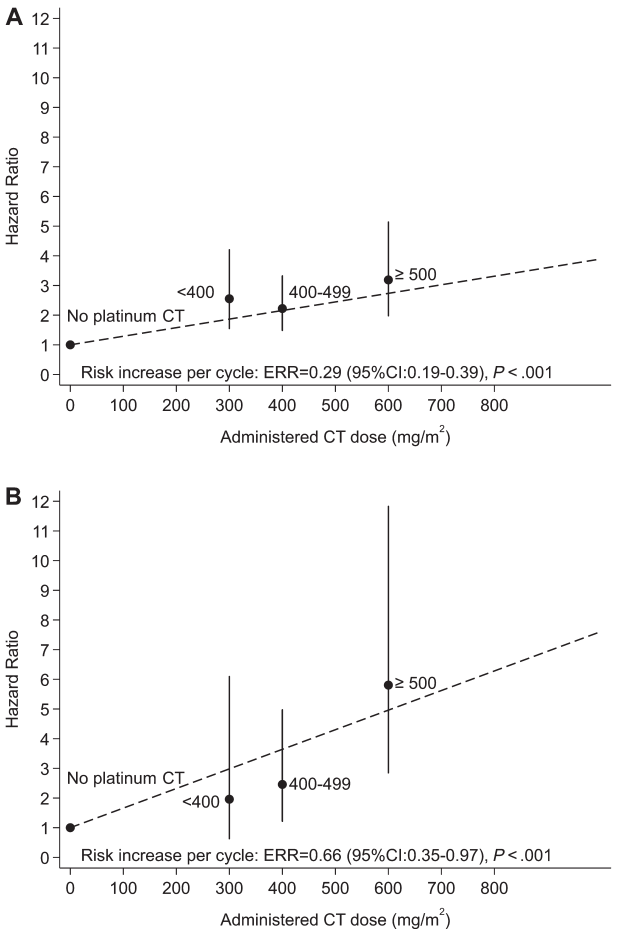

Figure 2. Mortality from (A) any SMNs and (B) gastrointestinal SMNs by the cumulative dose of platinum-containing CT (mg/m^2 of body surface area). HR estimates (ERRs) were derived from models adjusted for age (continuous), smoking at testicular cancer diagnosis, supradiaphragmatic radiotherapy, and subdiaphragmatic radiation dose. Circles represent HR estimates for dose categories (no platinum-containing CT and >0-399, 400-499, and ≥500 mg/m^2 of body surface area) and are plotted at the median dose in each category (0, 300, 400, and 600 mg/m^2, respectively). Dose-response relationships were based on the categorical dose as an outcome, with the category set at the median dose within that category. Vertical lines reflect the 95% CIs around the HRs for dose categories. The dashed line in panel A is the best fitting dose-response relationship and reflects a linear increase in the mortality risk from any SMN, with 0.29 (95% CI, 0.19-0.39; $P < .001$) added to the HR for each additional platinum-containing CT dose of 100 mg/m^2 body surface area. The dashed line in panel B is the best fitting dose-response relationship and reflects a linear increase in gastrointestinal SMN mortality risk, with 0.66 (95% CI, 0.35-0.97; $P < .001$) added to the HR for each additional platinum-containing CT dose of 100 mg/m^2 of body surface area. CI indicates confidence interval; CT, chemotherapy; ERR, excess relative risk; HR, hazard ratio; SMN, second malignant neoplasm.

times (95% CI, 0.9-4.1) after chemotherapy and tended to increase with an increasing administered dose of platinum-containing chemotherapy ($P_{trend} = .076$). Smoking at the TC diagnosis was an independent risk factor associated with 3.8 times increased lung cancer mortality (95% CI, 1.7-8.5). IHD mortality increased 2.1 times (95% CI, 1.5-4.2) after platinum-containing chemotherapy in comparison with patients without platinum exposure. IHD mortality also increased 3.4 times (95% CI, 1.4-8.3) among patients who smoked at the TC diagnosis.

The infradiaphragmatic radiation dose was also associated with increasing SMN mortality ($P_{trend} < .001$). Noncolorectal GI tract SMN mortality also increased with a higher infradiaphragmatic radiation dose. The administered infradiaphragmatic radiation dose showed a linear dose-response relationship, with the HR for any SMN increasing by 0.05 (95% CI, 0.03-0.07; $P_{trend} \leq .001$) and the HR for GI tract SMN mortality increasing by 0.12 (95% CI, 0.09-0.15; $P_{trend} \leq .001$) per gray of radiation administered (Fig. 3).

A complete case analysis, including only patients with nonmissing treatment data, showed similar results in comparison with the analysis incorporating imputed data. A sensitivity analysis with clustering on treatment center showed similar results for treatment-associated risks (Supporting Table 5).

DISCUSSION

In this large, multicenter cohort of Dutch patients with TC treated between 1976 and 2006, we observed increased mortality from SMNs as well as causes other than cancer, particularly IHD. Although a few studies previously reported increased mortality from solid SMNs, leukemia, and CVD among patients with TC, our study is the first to report that an increasing administered platinum dose is associated with a linearly increasing risk of SMN mortality, particularly mortality due to GI cancer.[6,8,15,26-28] Our study further adds to mortality estimates in previous studies by including primary and follow-up treatment and providing mortality risk estimates after more prolonged follow-up of patients treated with platinum-containing chemotherapy.

Both chemotherapy and radiotherapy have previously been associated with an increased risk of various solid SMNs, including GI and urologic malignancies.[5,6,19,26,29,30] Radiotherapy and chemotherapy were associated with SMN mortality (SMR for radiotherapy, 2.1; 95% CI, 1.8-2.5; SMR for chemotherapy, 2.5; 95% CI, 2.0-3.1). Our observation of an increasing risk of mortality due to SMNs with a higher cumulative dose of platinum-based chemotherapy is consistent with a dose-dependent increase in the solid SMN incidence, which we recently reported.[10] Kier et al[6] also recently

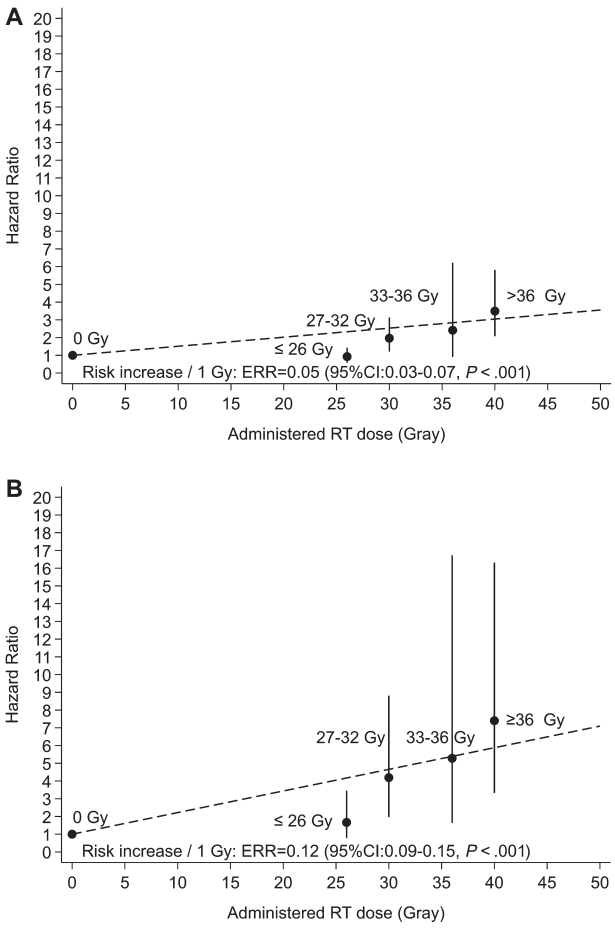

Figure 3. Mortality from (A) SMNs and (B) gastrointestinal SMNs by the administered infradiaphragmatic RT dose. HR estimates (ERRs) were derived from models adjusted for age (continuous), smoking at testicular cancer diagnosis, supradiaphragmatic RT, and platinum dose. Dose-response relationships were based on the categorical dose as an outcome, with the category set at the median dose within that category. Circles represent estimates for dose categories (no infradiaphragmatic RT and >0-26, 27-32, 33-36 Gy, and >36 Gy) and are plotted at the median dose in each category (0, 26, 30, 36, and 40 Gy, respectively). Vertical lines denote the 95% CIs around the HRs for dose categories. The dashed line in panel A is the best fitting dose-response relationship and reflects a linear increase in SMN mortality, with 0.05 (95% CI, 0.03-0.07; $P < .001$) added to the HR for each additional gray of infradiaphragmatic RT. The dashed line in panel B is the best fitting dose-response relationship and reflects a linear increase in gastrointestinal mortality, with 0.12 (95% CI, 0.09-0.15; $P < .001$) added to the mortality rate for each additional gray of infradiaphragmatic RT. CI indicates confidence interval; ERR, excess relative risk; HR, hazard ratio; RT, radiotherapy; SMN, second malignant neoplasm.

reported 1.6-fold increased SMN mortality among patients with TC treated with platinum-containing chemotherapy; risks were up to 5.8-fold increased among patients treated with multiple lines of treatment in comparison with general population controls. In their study, BEP chemotherapy was associated with increased mortality from lung, esophageal, and bladder cancers, soft-tissue sarcomas, and myeloid leukemia. We confirm their findings, but our observations include renal cancer rather than bladder cancer.

Cisplatin has been classified as a carcinogenic compound and acts by crosslinking DNA.[31,32] Previously, increased GI cancer incidence among childhood cancer survivors has been reported after platinum exposure.[33-35] Exposure to platinum-containing chemotherapy has been suggested to cause GI polyposis in humans, although the causal mechanism has not yet been established.[36]

Increased mortality from soft-tissue sarcomas was observed among patients with nonseminoma. Our results are in line with those of Kier et al,[6] who observed an increased risk of soft-tissue sarcoma after the receipt of BEP (median time, 12 years), whereas no increased risks were observed after radiotherapy. Our soft-tissue sarcoma cases died after a median follow-up of 10.6 years after primary TC. We cannot exclude the idea that the high SMR for sarcomas is partly due to late relapses, however rare.[37]

Radiotherapy was also associated with increased mortality from non-TC SMNs, and mortality remained increased throughout follow-up. Previous studies, which largely consisted of patients treated before the 1980s, found a 1.5 to 1.9 times increased SMR from SMNs after radiotherapy.[8,26,27] Excess mortality among irradiated patients with seminoma followed beyond 15 years is consistent with a radiation effect.[8,26] Robinson et al[4] observed excess cancer mortality only within the first 5 years after the diagnosis among patients treated with modern radiation techniques since the 1990s. A more recent Danish population-based study observed 2.1 times increased SMN mortality, particularly from stomach, pancreatic, prostate, and bladder cancers, after radiation for TC between 1984 and 2007.[6] Except for prostate cancer, we also observed increased mortality for these malignancies in our patients with seminoma.

A substantial proportion of all cancer deaths in our cohort among patients with seminoma was attributable to pancreatic cancer (18 deaths; 31% of SMN-related excess deaths), a malignancy with a poor prognosis that has not improved much over the last decades. A recent study already reported a strongly increasing SMN risk with higher radiation doses to the pancreas (excess relative risk, 0.12 per gray of radiation).[30] Because few patients with seminoma nowadays undergo para-aortic radiation and radiation doses for these patients are also generally lower (<26 Gy), radiation-associated pancreatic cancer mortality will likely decrease in the near future. On the

other hand, we recently reported that platinum-containing chemotherapy may also increase pancreatic cancer risk.[9]

IHD mortality was associated with the receipt of platinum-containing chemotherapy in our study. In line with our findings, chemotherapy exposure increased circulatory disease mortality 1.4-fold in a large, international registry–based study including 38,907 patients treated after 1975.[15] Kier et al[6] noted borderline significantly increased circulatory disease mortality after the receipt of chemotherapy in comparison with the general population in Danish patients treated between 1984 and 2007. Interestingly, Fung et al[14] recently observed increased CVD mortality only during the first year of follow-up (based on only 6 cardiac deaths and 5 cerebrovascular disease deaths), although the median follow-up was only 6.5 years after chemotherapy in their study. Some case reports have described severe acute myocardial infarction[38,39] or stroke shortly after chemotherapy in TC survivors,[40] although these events are rare and usually not fatal. Differences in the underlying CVD risk factors, lifestyles, and prophylactic use of low-molecular-weight heparin to prevent platinum-associated thromboembolic events may underlie these heterogeneous findings with respect to CVD mortality.[41,42]

We found increased mortality from respiratory diseases, particularly pneumonia, after exposure to chemotherapy in our cohort. Our results are in line with those of Fossa et al,[15] who observed increased respiratory mortality due to lung fibrosis and pneumonitis among patients treated with primary chemotherapy after 1975. To our knowledge, bleomycin has not been associated with side effects other than lung fibrosis. Unfortunately, because the current study did not include sufficient numbers of patients who did not receive bleomycin (ie, patients treated with etoposide and platinum), we cannot completely ascribe the increased mortality risks to platinum exposure alone.

Strong features of the current study include its extended follow-up and the availability of detailed treatment data. Using time-dependent Cox regression, we were able to more precisely allocate observation time to primary and follow-up treatment, and this increased the reliability of our results in comparison with other studies based on primary treatment only. Limitations include the lack of risk factors for cancer and cardiovascular mortality (ie, lifestyle and smoking), although smoking behavior in our cohort is not likely to differ from that of the general population.[15] In addition, our analysis did not allow further analysis for genitourinary malignancies because of the low numbers of cases exposed to platinum. Despite our efforts to abstract compete treatment exposure information from the medical records, we had missing data on, among other things, the cumulative platinum dose and body size. However, because dose reductions were rare and the actual cumulative administered dose for patients for whom we had complete information on dose and body surface was highly comparable to the dose based on the number of administered cycles of chemotherapy, in all our analyses, we approximated the cumulative platinum dose with the number of administered cycles of chemotherapy. We acknowledge that we present many significance tests and, therefore, caution against overinterpretation of our findings, especially when they are based on P values $> .001$.

For 191 of the 226 patients (84.5%) who died of an SMN and for 31 of the 51 patients (60.8%) who died of IHD, detailed treatment data were available from the medical records. For most of the patients who had died of an SMN and for whom detailed treatment data were missing, the date of death was later than the date of last linkage with the Netherlands Cancer Registry and the date of last information from the GP. We also identified 18 new fatal IHD events (among the 51 patients who died of IHD) among patients without a known IHD history. For these patients, either the GP had not responded to our request for information or the date of death was later than the date of the last medical information that we had received from the GP. In the Netherlands, unfortunately, tracing back patients identified on the basis of data provided by the cause of death registry at Statistics Netherlands is not allowed because of the privacy laws. For these patients, treatment details were imputed.

Despite efforts to reduce the long-term toxicity of TC treatment, we observed no decrease in overall excess mortality or mortality due to cancers other than TC among more recently treated patients, although absolute excess mortality only modestly increased after 1995. However, noncancer mortality decreased over time. Fossa et al[15] previously reported a significantly increased SMR from causes other than cancer of 1.07 for patients treated before 1975 and of 1.04 for patients treated after 1975 in comparison with general population rates, and this indicated only a small mortality reduction over time. Finally, treatment-associated mortality may be partly due to (interactions with) environmental and lifestyle factors that also operate in the general population.

In conclusion, TC survivors treated in the platinum era experience increased mortality from SMNs in comparison with the general population, and this appears in part due to exposure to platinum-containing chemotherapy. This study also shows that exposure to

platinum-containing chemotherapy is associated not only with a dose-dependent increased SMN incidence but also increased mortality from SMNs. Future studies and more prolonged follow-up of patients treated more recently with 3 or fewer (B)EP cycles are needed to better assess whether low platinum doses indeed still increase the risk for non-TC mortality. In the meantime, potential strategies toward risk reduction (ie, screening for malignancies of the GI tract as well as [risk factors for] CVDs) are warranted among long-term survivors treated with higher doses of platinum or para-aortic radiation. In addition, through healthier lifestyle behaviors (particularly smoking cessation, reduction of alcohol intake, increased physical activity, and a healthy diet), mortality may be reduced.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Harmke J. Groot: Conception and design, collection and assembly of data, data analysis and interpretation, and manuscript writing. **Flora E. van Leeuwen:** Conception and design, collection and assembly of data, data analysis and interpretation, and manuscript writing. **Sjoukje Lubberts:** Collection and assembly of data and manuscript writing. **Simon Horenblas:** Provision of study materials or patients and manuscript writing. **Ronald de Wit:** Provision of study materials or patients and manuscript writing. **J. Alfred Witjes:** Provision of study materials or patients and manuscript writing. **Gerard Groenewegen:** Provision of study materials or patients and manuscript writing. **Philip M. Poortmans:** Provision of study materials or patients and manuscript writing. **Maarten C. C. M. Hulshof:** Provision of study materials or patients and manuscript writing. **Otto W. M. Meijer:** Provision of study materials or patients and manuscript writing. **Igle J. de Jong:** Provision of study materials or patients and manuscript writing. **Hetty A. van den Berg:** Provision of study materials or patients and manuscript writing. **Tineke J. Smilde:** Provision of study materials or patients and manuscript writing. **Ben G. L. Vanneste:** Provision of study materials or patients and manuscript writing. **Maureen J. B. Aarts:** Provision of study materials or patients and manuscript writing. **Katarzyna Jóźwiak:** Data analysis and interpretation and manuscript writing. **Alexandra W. van den Belt-Dusebout:** Collection and assembly of data and manuscript writing. **Jourik A. Gietema:** Provision of study materials or patients and manuscript writing. **Michael Schaapveld:** Conception and design, collection and assembly of data, data analysis and interpretation, and manuscript writing.

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